What Characteristics at Baseline Are Associated with the Glucose-lowering Effect of Colestimide in Patients with Type 2 Diabetes and Hypercholesterolemia According to Response to Treatment?

Tatsuya Suzuki¹, Misako Tsunoda-Kubota¹, Junya Aoyama¹, Shoko Futami-Suda¹, Masao Hashimoto¹, Yoshimasa Igari¹, Kentaro Watanabe¹, Yoshiaki Kigawa², Hiroshi Nakano¹ and Kenzo Oba¹

¹Department of Cardiovascular Medicine, Nippon Medical School
²Hanno Geriatric Hospital, Saitama

Abstract

Colestimide, an anion exchange resin, reportedly improves glycemic control in patients with type 2 diabetes. However, no studies of the glucose-lowering effect of colestimide have identified responders and nonresponders. In the present study, we compared glycemic control, lipids, and body-mass index (BMI) among patients with type 2 diabetes receiving colestimide (n=59) until 24 weeks after the start of treatment. Subjects were classified as responders to treatment (n=40), who showed a 15% or greater decrease in glycated hemoglobin (HbA1c) or a 20% or greater decrease in plasma glucose level or both after 24 weeks of colestimide treatment as compared with baseline; nonresponders showed HbA1c >11.5% or fasting plasma glucose (FPG) >250 mg/dL during the course of the study and <15% decrease in HbA1c levels or <20% decrease in FPG levels or both after 24 weeks of colestimide treatment as compared with baseline. In responders, FPG decreased significantly from 196 ± 91 mg/dL to 125 ± 47 mg/dL after 24 weeks (P<0.001), and HbA1c decreased from 9.1% ± 2.0% to 7.0% ± 0.9% (P<0.001). In nonresponders, HbA1c decreased significantly from 7.7% ± 2.9% to 7.6% ± 1.2% (P<0.05). Multiple logistic regression analysis revealed that baseline HbA1c and the presence of cholelithiasis were significant determinants of the response to colestimide treatment when corrected for sex, age, triglyceride levels, and BMI at baseline and the presence of fatty liver. In conclusion, baseline HbA1c and the presence of cholelithiasis have strong and independent influences on the glucose-lowering effect of colestimide.

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Key words: colestimide, diabetes, responders

Correspondence to Tatsuya Suzuki, MD, PhD, Division of Geriatric Medicine, Department of Internal Medicine, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8603, Japan
E-mail: t-suzuki@nms.ac.jp
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Introduction

Both diabetes and hypercholesterolemia are important risk factors for cardiovascular disease. Hypercholesterolemia and diabetes commonly coexist, and together, they double the risk of cardiovascular disease. Bile acid binding resins (BABRs) have been used to treat dyslipidemia. Moreover, many studies have shown that BABRs have both lipid-lowering activity and blood glucose-lowering activity. We have previously reported that colestimide, an anion exchange resin, improves glycemic control in patients with type 2 diabetes. One study has shown that baseline glycated hemoglobin (HbA1c) is the most important independent factor affecting the glucose-lowering effect of colestimide. However, to our knowledge, no studies of the glucose-lowering effect of colestimide have been performed to identify responders and nonresponders.

Hence, we performed a prospective study of colestimide in patients with type 2 diabetes and hypercholesterolemia to examine its effects on blood glucose levels and other clinical biochemical markers and to determine which characteristics at baseline are associated with the glucose-lowering effect of colestimide when used as a long-term treatment.

Materials and Methods

Subjects and Design

From February 2, 2001, to June 30, 2008, the present study was performed at the Nippon Medical School Hospital in 59 outpatients with type 2 diabetes and hypercholesterolemia (19 men and 40 women; mean age, 64 ± 10 years; mean duration of diabetes, 11.6 ± 9.3 years; mean body-mass index [BMI], 27.2 ± 5.0 kg/m²) in whom glucose levels were poorly controlled despite a weight-maintaining diet and treatment with oral hypoglycemic agents. All patients underwent a standardized interview and physical examination.

All patients were instructed to ingest 1,500 mg of colestimide twice daily, i.e., before breakfast and dinner. At the subjects’ visits to the hospital as outpatients, i.e., week 12, week 0 (week of administration onset), week 12, and week 24, fasting blood samples were obtained. Moreover, according to the definition of Bluher et al., subjects were defined as responders or nonresponders to treatment with colestimide as follows: responders showed a >15% decrease in HbA1c levels or a >20% decrease in fasting plasma glucose (FPG) levels or both after 24 weeks of colestimide treatment as compared with baseline; nonresponders showed HbA1c>11.5% or FPG>250 mg/dL during the course of the study and <15% decrease in HbA1c levels or <20% decrease in FPG levels or both after 24 weeks of colestimide treatment as compared with baseline.

At respective time points, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, FPG level in the early morning, and γ-glutamyl transpeptidase (γGTP) were determined. Levels of HbA1c were assayed with high-performance liquid chromatography (Auto AIC analyzer; Arkray, Inc., Kyoto, Japan). Values for AIC (%) were estimated using the National Glycohemoglobin Standardization Program (NGSP) equivalent values (%), which were calculated from the formula AIC (%)=1.02 × A1C (Japanese Diabetes Society) (%) + 0.25%. This formula takes into consideration the relation between A1C (Japanese Diabetes Society) (%) determined using the previous Japanese standard measurement method and A1C (NGSP). Levels of γGTP were determined with the L-γ-glutamyl-3-carboxy-4-nitroanilide method. Total bilirubin (TB) was measured with the vanadate oxidation method. Furthermore, BMI (body weight [kg]/height [m²]) was calculated.

Subjects were excluded if they were hospitalized during the observation period. Cholelithiasis was defined as evidence of gallstones on ultrasonography or computed tomography or both, and fatty liver was defined as parenchyma having echogenicity greater than that of the cortex of the right kidney on different probe positions, the presence of vascular blurring, and deep attenuation with a 3.5-MHz transducer. Abdominal ultrasonography was performed by experienced medical technologists who were unaware of the objectives of the study. Abdominal computed tomography was performed
Response to Colestimide Treatment

Table 1  Baseline characteristics of subjects who are divided into responders and nonresponders

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=40)</th>
<th>Nonresponders (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>15/25</td>
<td>5/14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65±10</td>
<td>63±11</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>12±10</td>
<td>11±7</td>
</tr>
<tr>
<td>Diabetic therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet alone</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>α-glucosidase inhibitor</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Biguanides</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Glitazones</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Insulin</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Statin</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Antihypertensive drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Angiotensin II receptor blockers</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>α1 blocker</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Alcohol consumption ≥20 g/day</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>22</td>
<td>9</td>
</tr>
<tr>
<td>Cholelihiasis</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD; NS, no significance

by experienced radiologists, who were unaware of the objectives of the study. All subjects were instructed to continue their previous diet therapy and kinesitherapy without modification. Furthermore, drugs known to affect glucose tolerance or lipid control were not be added during the 24 weeks of treatment with colestimide. Subjects who had complete biliary obstruction or hyperbilirubinemia were excluded.

Before the start of the study, informed consent was obtained from all subjects after a sufficient explanation had been provided. The present study was designed in compliance with the ethics regulations set out by the Declaration of Helsinki.

Statistical Analysis

All data are presented as means ± SD. Paired t-tests and Wilcoxon’s rank-sum test were performed to compare data obtained before and after colestimide treatment. The χ² test was performed for categorical variables. Statistical analysis of the data was performed with the Mann-Whitney U test, Pearson’s correlation, and multiple logistic regression analysis. A value of P<0.05 was considered to indicate statistical significance. All statistical tests were performed with a statistical software program (IBM SPSS Statistics, version 12, IBM Corp., Armonk, NY, USA). Furthermore, the last observation carried forward method was used to handle any missing values.

Results

At baseline, 32 of the 59 subjects had hypertension; 26 had received a hydroxymethyl glutaryl coenzyme A reductase inhibitor (statin); 7 consumed 1 or more alcoholic drinks (20 g) per day, according to the modified definition of Doi et al.12; 31 had fatty liver; and 16 subjects had cholelihiasis. At baseline responders and nonresponders did not differ significantly with respect to sex, mean age, duration of diabetes, use of antihypertensive drugs or statins, alcohol consumption, or the frequency of fatty liver. However, the frequency of cholelihiasis was significantly higher in responders than in nonresponders (Table 1).

Diachronic changes observed in each variable between before and after treatment with colestimide at respective time points are shown in Table 2. Significant decreases from just before the start of
Table 2 Change in clinical biochemical markers at -12 weeks, baseline, 12 weeks, and 24 weeks with colestamide treatment

<table>
<thead>
<tr>
<th>Subjects (n=59)</th>
<th>-12 weeks</th>
<th>0 week</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>177±73</td>
<td>184±88</td>
<td>140±73***</td>
<td>131±46***</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.3±2.0</td>
<td>8.4±1.6</td>
<td>7.2±1.1***</td>
<td>7.2±1.1***</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>225±32</td>
<td>226±34</td>
<td>202±33***</td>
<td>200±32***</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>60±32</td>
<td>56±20</td>
<td>55±19</td>
<td>58±25</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>189±169</td>
<td>178±117</td>
<td>183±129</td>
<td>168±97</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7±6.0</td>
<td>27.1±5.5</td>
<td>26.5±4.4*</td>
<td></td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>39±55</td>
<td>40±42</td>
<td>38±47</td>
<td>38±54</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.61±0.29</td>
<td>0.66±0.36</td>
<td>0.64±0.33</td>
<td>0.62±0.30</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*: Baseline vs P<0.05, **: Baseline vs P<0.01, ***: Baseline vs P<0.001
FPG, fasting plasma glucose; HDL cholesterol; high-density lipoprotein cholesterol, HbA1c; glycated hemoglobin, BMI; body-mass index; γ-GTP, γ-glutamyl transpeptidase

Table 3 Changes in clinical biochemical markers at -12 weeks, baseline, 12 weeks, and 24 weeks in responders and nonresponders

<table>
<thead>
<tr>
<th>Responders (n=40)</th>
<th>-12 weeks</th>
<th>0 week</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>194±77</td>
<td>196±91 †</td>
<td>141±83***</td>
<td>125±47***</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>9.0±2.1</td>
<td>9.1±2.0 †</td>
<td>7.1±1.0***</td>
<td>7.0±0.9***</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>222±31</td>
<td>227±32</td>
<td>202±35***</td>
<td>198±29***</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>56±22</td>
<td>51±18</td>
<td>52±17</td>
<td>59±29</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>200±169</td>
<td>191±116</td>
<td>196±138</td>
<td>175±84</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.0±5.4</td>
<td>27.6±4.2</td>
<td>27.3±3.6*</td>
<td></td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>41±56</td>
<td>45±45</td>
<td>42±51</td>
<td>39±58</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.65±0.34</td>
<td>0.70±0.40</td>
<td>0.67±0.38</td>
<td>0.60±0.28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonresponders (n=19)</th>
<th>-12 weeks</th>
<th>0 week</th>
<th>12 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>144±50</td>
<td>146±48</td>
<td>143±42</td>
<td>143±43</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0±1.6</td>
<td>7.7±2.9</td>
<td>7.5±1.2*</td>
<td>7.6±1.2*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>228±34</td>
<td>230±30</td>
<td>203±26**</td>
<td>201±38*</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>69±42</td>
<td>62±23</td>
<td>65±25</td>
<td>59±18</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>188±183</td>
<td>140±100</td>
<td>150±100</td>
<td>140±124</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8±8.3</td>
<td>25.4±6.0</td>
<td>24.8±5.4</td>
<td></td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>37±55</td>
<td>31±24</td>
<td>32±34</td>
<td>35±45</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.55±0.19</td>
<td>0.59±0.29</td>
<td>0.58±0.21</td>
<td>0.67±0.35</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SD.

*: Baseline vs P<0.05, **: Baseline vs P<0.01; ***: Baseline vs P<0.001
†, ††, †††: P<0.05 vs nonresponders; †‡, ††‡, †††‡: P<0.01 vs nonresponders.
FPG, fasting plasma glucose; HDL cholesterol; high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; BMI, body-mass index; γ-GTP, γ-glutamyl transpeptidase

Treatment (0 week) were observed in the values of the following variables: FPG after 12 weeks and 24 weeks, HbA1c after 12 weeks and 24 weeks, BMI after 24 weeks, and total cholesterol concentrations after 12 and 24 weeks. However, no significant changes were observed in HDL cholesterol, triglycerides, γ-GTP, or TB.

Table 3 shows changes in clinical biochemical markers at -12 weeks, baseline, 12 weeks, and 24 weeks in responders and nonresponders. At baseline, FPG levels and HbA1c were significantly higher in responders than in nonresponders (p<0.01,
Response to Colestimide Treatment

Table 4  Multiple logistic regression analysis of responder/nonresponder by colestimide in relation to other variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coefficient (b)</th>
<th>Odds ratio</th>
<th>95%CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>-0.276</td>
<td>0.739</td>
<td>0.084–6.870</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>-0.013</td>
<td>0.987</td>
<td>0.903–1.079</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c at baseline</td>
<td>0.864</td>
<td>2.373</td>
<td>1.150–4.896</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Triglyceride at baseline</td>
<td>0.007</td>
<td>1.007</td>
<td>0.997–1.018</td>
<td>NS</td>
</tr>
<tr>
<td>BMI at baseline</td>
<td>0.169</td>
<td>1.184</td>
<td>0.928–1.509</td>
<td>NS</td>
</tr>
<tr>
<td>Fatty liver</td>
<td>-0.624</td>
<td>0.536</td>
<td>0.066–4.322</td>
<td>NS</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>3.060</td>
<td>21.33</td>
<td>1.465–310.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Full-model R²: 0.374 (adjusted); NS, no significance
HbA1c, glycated hemoglobin; BMI, body-mass index

p<0.05, respectively). However, no significant differences were found between responders and nonresponders with respect to levels of total cholesterol, HDL cholesterol, triglycerides, γGTP, TB, or BMI. In responders, significant decreases were observed in FPG after 12 and 24 weeks treatment, HbA1c after 12 and 24 weeks, BMI after 24 weeks, total cholesterol concentrations after 12 and after 24 weeks, but no significant change before and after administration were observed in HDL cholesterol, triglycerides, γGTP, or TB. In nonresponders, no significant differences were found between before and after treatment with respect to any biochemical marker, except for HbA1c and total cholesterol concentrations.

A response to colestimide treatment showed significant correlation with FPG at baseline, the presence of cholelithiasis, and HbA1c level at baseline (Pearson correlation coefficient: r=0.300, p<0.05; r=0.267, p<0.05, r=0.294, p<0.05; respectively), but there was no such correlation with other markers.

Multiple logistic regression analyses, when corrected for female sex, age, triglyceride levels at baseline, and BMI at baseline, and the presence of fatty liver showed that the response to colestimide treatment was significantly and positively associated with HbA1c level at baseline and the presence of cholelithiasis (Table 4).

Discussion

The present study found that FPG and BMI decreased significantly after treatment with colestimide in all subjects and in subjects classified as responders to treatment. Baseline HbA1c and the presence of cholelithiasis had strong and independent influences on the glucose-lowering effect of colestimide.

Colestervelam, another BABR, has been approved by the United States Food and Drug Administration for use as an antihyperglycemic agent, and many studies have confirmed its glucose-lowering effect. However, colestimide has not been approved as an antidiabetic medication in Japan. Hence, no studies in Japan have examined which characteristics at baseline are associated with the glucose-lowering effect of colestimide, when used as a long-term treatment, according to subjects’ status as responders or nonresponders.

In the present study, treatment with colestimide produced significant decreases in FPG after 12 weeks and 24 weeks, in HbA1c after 12 weeks and 24 weeks, and in BMI after 24 weeks. Furthermore, when subjects were classified as responders or nonresponders according to the definition of Bluher et al., we found that responders had a higher HbA1c and a higher rate of cholelithiasis at baseline. Our results were consistent with those of another study that found that baseline HbA1c was the most important predictor of the effectiveness of colestimide therapy. Moreover, we found that responders to colestimide were more likely to have cholelithiasis before the start of treatment. This finding is consistent with a previous study that found that gallbladder disease is strongly associated
with insulin resistance, because patients with
gallbladder disease are likely to have metabolic
disorders, such as diabetes, hypertension,
hypercholesterolemia, and obesity.8-10

Although the mechanism by which colestimide
decreases blood glucose levels remains unclear,
glucose-like peptide 1 (GLP-1) induced by colestimide
plays an important role in glucose metabolism, as we
previously reported that colestimide increases the
secretion of GLP-1.11 Recently, TGR5, a G protein-
coupled receptor, which, upon binding by bile acids,
stimulates downstream cyclic adenosine
monophosphate (cAMP) signaling pathways in a
wide array of tissues and cell types, is reported to
represent an essential component in the pathway
mediating the enhanced GLP-1 release in response to
colestimide.12 Furthermore, enhanced GLP-1
secretion has been proposed as a mechanism of the
glucose-lowering action of BABRs.13-14

Another possible contributor to the effects of
colestimide is the gastrointestinal hormone
cholecystokinin. Colestyramine is reported to
increase cholecystokinin,15 and incretins, such as
cholecystokinin, reportedly have hypoglycemic
effects.8 Because colestimide acts in the intestine, as
does colestyramine, we can speculate that
colestimide also affects gastrointestinal hormones,
through which its hypoglycemic effects are
produced. However, our previous study found no
relationship between the blood glucose-lowering
activity of colestimide and serum concentrations of
cholecystokinin in patients with type 2 diabetes,
perhaps because the intervals between
measurements were too long.8

In the present study, mean BMI decreased
significantly in all subjects and in subjects who
responded to colestimide. In our previous study,
body weight decreased significantly at week 12 of
colestimide administration; furthermore, visceral fat
accumulation also decreased significantly.8 However,
BABRs have been reported to cause no change in
body weight.16-17 On the other hand, preclinical
studies in mice have documented the body weight-
reducing effect of colestimide.8 Why the results are
different in humans remains unknown. A recent
study has shown the possible presence of brown
adipose tissue in many adults.8 We suspect that the
susceptibility to changes in the cholic acid ratio of
the serum bile acid composition differs in humans
due to the so-called TGR5-cAMP-D2 pathway. The
effects of colestimide on body composition and
brown adipose tissue should be investigated in a
large number of obese patients with type 2 diabetes.

Nevertheless, the present study had several
limitations. First, this study was a pilot study with a
small number of subjects and was not placebo-
controlled. Furthermore, selection bias was present
because the subjects were outpatients. Second, we
did not assess visceral fat area or abdominal
circumference at the umbilicus. Third, we did not
measure levels of immunoreactive insulin and
adipocytokines. Therefore, a long-term, large-scale,
placebo-controlled clinical trial of colestimide should
be performed. Last, because abdominal
ultrasonography is useful for detecting cholelithiasis
and fatty liver, it should be performed in every
subject in the future.

In conclusion, baseline HbA1c and the presence of
cholelithiasis have strong and independent effects on
the glucose-lowering effect of colestimide.

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controlled pilot study evaluating the effect of
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